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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/620,451	07/17/2003	John P. Dalton	1181-281	9171

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EXAMINER	
DUFFY, PATRICIA ANN	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 11/07/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/620,451	DALTON ET AL.	
	Examiner	Art Unit	
	Patricia A. Duffy	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) *12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *7-17-03* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 08/424,361.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The response and amendment to the claims filed July 25, 2006 has been entered into the record. Claims 1-12 are pending.

Sequence Requirements

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. § § 1.821-1.825 because the recited sequences in the specification are not followed by a particular sequence identifier. See pages 13 and 25.

Priority

Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). The certified copies have been filed in parent Application No. 08/424,361, filed on May 25, 1995.

Drawings

The drawings in this application have been accepted. No further action by Applicant is required.

Specification

The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

The specification lacks a section entitled "Brief Description of the Figures".

Brief Description of the Several Views of the Drawing(s): See MPEP § 608.01(f).

A reference to and brief description of the drawing(s) as set forth in 37 CFR 1.74.

The use of the trademark NOVASOME™ has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Information Disclosure Statement

The information disclosure statement filed 7-17-03 has been considered. An initialed copy is enclosed.

Election/Restrictions

Applicant's election of Group I in the response filed July 25, 2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Upon reconsideration claim 11 is rejoined to Group I.

Claim 12 is withdrawn from consideration as a non-elected invention.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 7 and 11 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

The claimed invention is drawn to a protein product of nature. Products of nature are not patentable because they do not reflect the "hand of man" in the production of the product or manufacturing process. Diamond v. Chakrabarty, 206 USPQ 193 (1980). Additionally, purity of naturally occurring product does not necessarily impart patentability. Ex parte Siddiqui 156 USPQ 426 (1966). However when purity results in new utility, patentability is considered. Merck Co. V. Chase Chemical Co. 273 F. Supp 68 (1967). See also American Wood v. Fiber Disintergrating Co., 90 US 566 (1974); American Fruit Growers v. Brogdex Co. 283 US 1 (1931); Funk Brothers Seed Co. V. Kalo Innoculant Co. 33 US 127 (1948). Filing of arguments and evidence of a new utility imparted by the increased purity of the claimed invention *and amendment to the claims to recite the essential purity* of the claimed products is suggested to obviate this rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an immunogenic composition comprising a *Fasciola hepatica* cathepsin L protease wherein said cathepsin L protease has a molecular weight of 29 kDa by sodium dodecyl sulphate polyacrylaminde gel electrophoresis under reducing conditions and is at least 95% pure and an adjuvant or a 95% pure cathepsin L *Fasciola hepatica* cathepsin L protease that has a molecular weight of 29 kDa by sodium dodecyl sulphate polyacrylaminde gel electrophoresis under reducing conditions and associated methods, it does not does not reasonably provide enablement for vaccines, antigenic fragments or epitopes thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are drawn to vaccines and methods of use comprising any Fasciola hepatica protein as having cathepsin L2 activity and at least 95% pure or an antigenic fragment or epitope thereof. The art or IUBMB Enzyme nomenclature does not recognize a sub-category of cathepsin L proteases called cathepsin "L2's". As such, the recitation of "L2" does not distinguish the claimed cathepsin L2 from other cathepsin L's.

The specification is limited to the showing of a purified *Fascioloa hepatica* cathepsin L2 protease wherein said cathepsin L2 protease has a molecular weight of 29 kDa by sodium dodecyl sulphate polyacrylaminde gel electrophoresis under reducing conditions wherein the cathepsin L2 protease is an excretory/secretory protein obtained from culture supernatants. The specification does not teach intracellular cathepsin L2 proteases or how to purify such, nor does the specification teach that the claimed composition or any other composition comprising any *Fasciola hepatica* cathepsin L2 protease or antigenic fragment or epitope is sufficient to provide for protecting disease and is effective in combating a parasitic infestation of helminiths (genus) in a mammal. The specification is devoid of any showing that the claimed protease is (a) immunogenic and (b) protective for *Fasciola hepatica* or any other helminith as claimed.

The dictionary definition of vaccine is "A prophylactic or therapeutic material containing antigens derived from one or more pathogenic organisms which, on administration to man or animal, will stimulate active immunity and protect against infection with these or related organism (i.e. produce protective immunity)." (The Dictionary of Immunology, Herbert et al eds, Academic Press, 1995) would clearly realize the critical deficiency of this specification with respect to vaccines. There is no demonstration of protective immunity upon administration in any animal model of helminith disease using the claimed composition. Such is required by the common meaning as demonstrated by the dictionary definition and is reiterated in Plotkin et al, as is cited in the previous office action. Further, as previously set forth none of the art recognized homologs have been demonstrated to have vaccine properties with the homologous microorganism. The art is replete with evidence that the ability to produce an antibody (immunogenicity) is insufficient to correlate with protection from infection. See for example Feng et al (Infection and Immunity, 64(1):363-365, 1996) that teaches that P55, is an immunogenic but nonprotective 55-kilodalton *Borrelia burdorferi* protein in murine lyme disease. Additionally, the art teaches "Although many investigators have tried to develop vaccines based on specific antigens, it is well understood that the ability of an antigen to stimulate antibody production does not necessarily correlate with the ability of the antigen to stimulate an immune response capable of protecting an animal from infection, particularly in the case of parasite helmiths. Although a number of prominent antigens have been indentified in several parasitic helminiths, there is yet to be a commercially available vaccine developed for any parasitic helminith." (Chandrashekar et al, US Patent No. 6,248,329, B1, column 1, lines 35-45). The teachings of the specification are devoid of any teaching that animals in a normal infection generate antibodies that bind the polypeptide(s) as claimed and therefore is not clear that the polypeptides of the invention are capable of generating an antibody response during a normal course of infection. Further, the specification fails to teach that any immune response generated

upon injection by the claimed polypeptides, alone or in combination with other antigens provide for a protection against infection. Vaccines by definition trigger an immunoprotective response in the host vaccinated and mere antigenic response is insufficient. It is well recognized in the vaccine art, that it is unclear whether an antigen(s) derived from a pathogen will elicit protective immunity. Ellis, R.W. (Chapter 29 of "VACCINES" [Plotkin, S.A. et al. (eds) published by W. B. Saunders company (Philadelphia) in 1988, especially page 571, 2nd full paragraph] exemplifies this problem in the recitation that "The key to the problem (of vaccine development) is the identification of that protein component of a virus or microbial pathogen that itself can elicit the production of protective antibodies.... and thus protect the host against attack by the pathogen". The specification fails to teach that the claimed polypeptides or fragments or epitiopes thereof alone or in combination with other antigens does in fact confer protection from infection, as is requisite of a vaccine composition. The art teaches that the selection of protective antigens from the plethora of protein antigens available is unpredictable. The specification fails to that the presence of antibodies that bind *Fasciola hepatica* cathepsin L2 protease wherein said cathepsin L2 protease has a molecular weight of 29 kDa by sodium dodecyl sulphate polyacrylaminde gel electrophoresis under reducing conditions as claimed, provides for protection from homologous infection by the parasite *Fasciola hepatica* or heterologous infection by a different parasitic helminith. The specification lacks specific written description of antigenic fragments or epitopes of any cathepsin L2 protease. One could not make such, because these fragments are not described in the specification. The courts have held that it is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of an invention in order to constitute adequate enablement. (Genentech Inc. v. Novo Nordisk A/S Ltd., 42 USPQ2d 1001). Moreover, the specification must have been enabling at the time the invention was made and developments after the time of filing are of no consequence to what one skilled in the art would have believed at the time

of filing (*In re Wright*, 27 USPQ2d 1510). In the absence of a teaching of the claimed polypeptides are effective in prevention of disease, the specification is not be enabled for vaccines. In view of the unpredictability of the art, the lack of teachings of the specification, it would require undue experimentation on the part of the skilled artisan to practice the invention as claimed.

With respect to claims 7 and 11, the specification does not provide written description of the "cathepsin L2" from other flukes, other parasites, other organisms which include mammals. The specification does not describe how to purify the cathepsin L2 fro m these other sources. The purification of individual proteins is highly empirical in nature. The skilled artisan requires key characteristics pf the protein and/or critical purification steps before even preliminary purification approaches can be devised. The steps of protein purification are different for each protein and vary a great deal from protein to protein. There are hundreds of individual purification procedures and exponential combinations thereof. There is no one single purification method for different proteins. As such, the purification method disclosed for the disclosed enzyme protein, would not arguably work for any other protein. The specification does not teach that this purification method allows the isolation of any of a variety of different enzymes. General methods described do not provide specific guidance needed for particular proteins. The art teaches that "One should not read published descriptions of successful purification and cloning attempts, or review of methods useful in the attempts, and presume that cloning and protein purification is a routine approach with the person of ordinary skill practices like falling off a long one given a published description of an assay for a protein. A description of an assay for a protein does not teach or suggest any particular characteristic of the protein that would assist the skilled artisan in its purification, such as pI, size, shape, etc. General methods described in a review contain no hint of suggestion about the necessary approach for the actual purification of a specific protein. The requirements of purification vary so much from protein to protein, that the

knowledge gained from purifying one protein can be useless in devising a protocol to purify another, and in fact a detergent or other element used successfully in one protocol can inactive or destroy another protein." (BIO Critical Synergy: The Biotechnology Industry and Intellectual Property Protection, Biotechnology Industry Organization, Presentations October 17, 1994, page 75-107, page 105, second full paragraph in particular). As such, one of skill in the art would have substantial reason to doubt that the protocol devised for purification of the disclosed species from *F. hepatica* supernatant is not broadly applicable to any enzyme from any source as is now claimed. The specification does not place any structure, chemical or functional limitations on the variants of cathepsin L2. The scope of the claims includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted. Structural features that could distinguish compounds in the genus of cathepsin "L2" from others in the protein class of "cathepsin L's" are missing from the disclosure and the claims. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description, because specific, not general guidance is needed. Since the disclosure fails to describe the common attributes or structural characteristics that identify members of the genus, and because the genus is highly variant, the function of "cathepsin L2" alone is insufficient to describe the genus of polypeptides of that function equivalently. One of skill in the art would reasonable conclude that the disclosure of a single cathepsin L2 from *F. hepatica* having the N-terminal sequence of SEQ ID NO:23 and the molecular weight of 29kDa by SDS-reducing gel, fails to provide a representative number of species to describe the claimed genus which is drawn to any enzyme derived from any source. Therefore, the skilled artisan would readily appreciate that applicants were not in possession of the claimed genus because the specification does not convey to one of skill in the art a representative number of variants from different sources. The genus of polypeptides with the claimed function is substantial and highly variant because the polypeptides do not

have a common structure and function. The recitation of "cathepsin L2" does not convey a common structure nor a common function, because the recitation of "L2" does not impart a function that is unique to a subgroup of cathepsin L enzymes. As such, generic enzymes that are unrelated via structure and function are highly variant and not conveyed by way of written description by the specification at the time of filing. The specification lacks written description for the highly variant genus of single function polypeptides (cathepsin L2 activity) and one skilled in the art would not recognize that applicants had possession of the genus of claimed enzymes as instantly claimed. Further, the specification does not teach the complete amino acid sequence of the identified cathepsin L proteases and as such, does not describe the corresponding nucleic acid sequences. Therefore, the skilled artisan would clearly recognize that Applicants were not in possession of any cathepsin produced by recombinant DNA techniques, because the DNA was not described in the specification as filed.

Claims 1-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims recite "cathepsin L2" or "cathepsin L2 activity". The art and IUBMB Enzyme nomenclature does not recognize a sub-category of cathepsin L proteases called cathepsin "L2's" (see NiceZyme View of Enzymes) The recitation of "L2" does not distinguish the claimed cathepsin L2 from other cathepsin L's having the same enzymatic activity and inhibitor characterization. Therefore, the skilled artisan would not be readily apprised and able to appreciate the metes and bounds of a cathepsin "L2" from any other cathepsin "L".

Claim Rejections - 35 USC § 102 and 103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4, 7 and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Dowd et al (Biochemical Society Transactions 20:1(86S (Feb 1991).

Dowd et al teach a cathepsin L, purified from *Fasciola hepatica*. Dowd et al teach that antisera was prepared from the cathepsin L excised from SDS PAGE gels. The pure cathepsin L in the SDS-PAGE gel is a good immunogen. The SDS-PAGE provides for adjuvant activity. Since cathepsin L2 is not conventional nomenclature for specific subset of cathepsin L's and is not specifically defined in the specification, the composition of the prior art isolated purified cathepsin L in the SDS-gel inherently meets the claims absent factual evidence to the contrary. The recited N-terminal sequence is inherent to the purified protein.

Claims 7 and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Dowd et al (Mol. Biochem. Parasitol. 35:161-166, 1989).

Dowd et al teach several isolated cathepsin L enzymes for *F. hepatica*. The enzymes were inhibited by leupeptin and E-64 classic inhibitors of cyesteine/thiol proteases of the cathepsin L type.

Claim 11 is rejected under 35 U.S.C. 102(b) as being anticipated by Rege et al (molecular and Biochemical Parasitiology 35:89-96, 1989).

Rege et al teach several isolated cysteine proteases of *F. hepatica* of the cathepsin L type that were inhibited by leupeptin, iodoacetate and Ep459. The enzymes were inhibited by leupeptin and E-64 classic inhibitors of cyesteine/thiol proteases of the cathepsin L type.

Status of the Claims

Claims 1-11 stand rejected. Claim 12 is withdrawn from consideration.

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy whose telephone number is 571-272-0855. The examiner can normally be reached on M-Th 6:30 am - 6:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's Acting Supervisory Examiner Mark Navarro can be reached on 571-272-0861.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patricia A. Duffy, Ph.D.

Primary Examiner

Art Unit 1645